201-14985

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

COMMERCIAL HYDROXYETHYLPIPERAZINE

CAS NO. 000103-76-4

Prepared by:

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EXECUTE SUMMARY

The Dow Chemical Company voluntarily submits the following screening information data and Test Plan covering the commercial product Hydroxyethylpiperazine, also known as Commercial HEP (CAS No. 000103-76-4), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

Commercial HEP is a mixture of the original starting ingredients, piperazine and water, and hydroxyethylpiperazine and dihydroxyethylpiperazine. Commercial HEP meets EPAs definition of a closed system intermediate. Some data exists on the mixture, Commercial HEP, as well as piperazine (PIP), hydroxyethylpiperazine (HEP) and dihydroxyethylpiperazine (DHEP). Robust summaries of available data for relatively pure hydroxyethylpiperazine (HEP) and Commercial HEP are provided as is limited information for dihydroxyethylpiperazine (DHEP). A complete SIDS data package exists for piperazine which is undergoing an EU Risk Assessment. A draft EU Risk Assessment containing more information is also appended. A robust dossier for piperazine will be prepared by the Swedish authorities in the near future and will be added to the data package when available. Based on the available data for piperazine and limited data on the mixture or other components, only a chromosomal aberration test (OECD 473) and reproduction/developmental toxicity study (OECD 421) of Commercial HEP are needed.

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TEST PLAN FOR COMMERCIAL HYDROXYETHYLPIPERAZINE

CAS Nos. 103-76-4

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Commercial Hydroxyethylpiperazine (Commercial HEP). The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of Commercial HEP, as defined by the Organization for Economic Cooperation and Development (OECD). Since Commercial HEP is a mixture of piperazine (PIP), hydroxyethylpiperazine (HEP), dihydroxyethylpiperazine (DHEP) and water, information on the pure materials are provided whenever possible. The information provided comes from existing data developed by or on behalf of Dow or found in the published scientific literature and fulfills Dow's obligation to the HPV Challenge Program.

A. Composition

	CAS Reg. No.
Hydroxyethylpiperazine	000103-76-4

Composition of Commercial HEP

Chemical	CAS #	Percentage
Hydroxyethylpiperazine	103-76-4	38-47
bis-Dihydroxyethylpiperazine	122-96-3	16-25
Piperazine	110-85-0	12-20
Water	7732-18-5	17-26

B. Manufacturing & Use

HEP does not occur naturally. HEP for commercial sale is made by adding ethylene oxide (EO) to an aqueous solution of Piperazine. The resulting product contains HEP as the most abundant component, along with unreacted piperazine (12-20%), water from the initial piperazine solution (17-26%), and bis-(hydroxyethyl)piperazine (16-25%), another co-product of the PIP-EO reaction. No further refining is done, and the product is shipped as Commercial HEP. This product is used primarily as the raw material in a process for producing triethylenediamine (TEDA) - a widely used urethane catalyst. A small amount is used in the removal of acid gases from natural gas streams. Thus the number of customers is fairly limited and Commercial HEP meets the EPA definition of a closed system intermediate.

Based on the uses of Commercial HEP, exposure to this product will be very limited and is only expected to

occur in manufacturing sites of HEP or TEDA. The Dow Chemical Company is unaware of Commercial HEP being sold into consumer applications in the US.

Due to the corrosive nature and sensitization potential of the material, personal protective equipment is recommended whenever possibility of exposure may occur. This can include a positive pressure supplied air respirator, monogoggles, gloves and other protective clothing. The source of release to the environment is primarily manufacturing sites which could occur during upset conditions. Commercial HEP could potentially be released to surface water, air or soil from manufacturing sites during upset conditions. Residual levels of Commercial HEP could be present in TEDA. However, the levels of the components of Commercial HEP would be quite low.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either:
1) Internal studies conducted by/or for Dow
2) Studies that have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or
3) Studies that were estimated using environmental models accepted by the US EPA (1999b) for such purposes.

This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with Commercial HEP and when known PIP, HEP and DHEP. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VII. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:
1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).
3. Not Valid – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.
4. Not Assignable – Includes studies in which limited data is provided.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion:

A chromosomal aberration test (OECD 473) and reproduction/developmental toxicity study (OECD 421) of Commercial HEP are recommended.

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure and Water Solubility) have been measured for each component as well as for the mixture. The partition coefficient has only been measured for piperazine. The EPIWIN model predicts HEP and DHEP will have a lower Kow than piperazine and would concentrate in water. Thus no additional studies are necessary.

Environmental Fate values for Transport (Fugacity) and Photodegradation were obtained using computer estimation –modeling programs. Piperazine, HEP and DHEP will primarily accumulate in water with approximately 30% in soil. The photodegradation half life is $\leq$0.8 hours. The individual components of Commercial HEP are not expected to hydrolyze. Piperazine has been shown to be inherently biodegradable in an OECD 302B study. In a UCC study, PIP, HEP and DHEP were reported to undergo 11, 13 and 10% biodegradation after 20 days. Thus no additional studies are necessary.

Ecotoxicity studies have been conducted in aquatic organisms for piperazine and in daphnia for hydroxyethylpiperazine and dihydroxyethylpiperazine. Computer estimation modeling has been conducted for fish and algae for HEP and DHEP. The available data shows that daphnia are much more sensitive to piperazine than fish and algae. The available data also shows that daphnia are much less sensitive to HEP and DHEP than piperazine. Computer models predict that fish and algae are also less sensitive to HEP and DHEP than piperazine. Thus no additional studies are recommended.

Mammalian Toxicity Endpoints (Acute Toxicity and Ames Mutagenicity Data) have been considered adequate. Reproductive effects have been reported for piperazine and thus Commercial HEP is also considered to cause reproductive effects. Piperazine was negative in a rat developmental study and effects observed in rabbit developmental study were attributed to maternal toxicity. There is no developmental toxicity information available for HEP, DHEP or Commercial HEP. Since Commercial HEP meets the criteria of a closed system intermediate, the most cost effective study using the least number of animals would appear to be an OECD 421 reproduction/developmental toxicity study of Commercial HEP. Piperazine was negative in in vitro and in vivo chromosomal aberration studies. However no data is available for HEP, DHEP or Commercial HEP. Thus an OECD 473 chromosomal aberration test of Commercial HEP needs to be conducted.

In summary, based on the available data, a chromosomal aberration test (OECD 473) and dermal reproduction/developmental toxicity study (OECD 421) of Commercial HEP are recommended.

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VII of this dossier.

A. Chemical/Physical Properties

HPV Endpoints for Chemical/Physical Properties have been summarized (Table 1). Melting point, boiling point and vapor pressure data for pure PIP, HEP or DHEP are different than for Commercial HEP. This is due to the high water concentration remaining in the commercial product. Log Kow is measured for PIP, estimated for HEP and DHEP with all values less than one which suggests that the material will not bioconcentrate. Commercial HEP and it's major components are highly water soluble.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with CMME. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

HPV Endpoints for Environmental Fate have been summarized (Table 2). PIP, HEP and DHEP are not expected to hydrolyze in water. The photodegradation half life for PIP is approximately 0.8 hours. Piperazine has been shown to be inherently biodegradable in an OECD 302B study. In a UCC study, PIP, HEP and DHEP were reported to undergo 11, 13 and 10% biodegradation after 20 days. Thus no additional studies are necessary.

Conclusion – Based on the available data and modeling, no additional testing is recommended.

C. Aquatic Toxicity

HPV Endpoints for aquatic toxicity data have been summarized (Table 3). Data is available for PIP as regards fish, daphnia and algae acute toxicity. This data demonstrates that daphnia are much more sensitive than fish or algae to PIP. Daphnia are less sensitive to HEP or DHEP than PIP.

Although no fish and algae acute toxicity data exists for HEP and DHEP, modeling using the ECOSAR program would suggest that aquatic toxicity is less of a concern for HEP and DHEP than for PIP.

Conclusion – Based on the available data and modeling, no additional testing is recommended.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 4 and 5. Except for PIP, each report has been further summarized in the Robust Summary section of this Dossier.

1.0 Acute Toxicity

The acute oral and dermal LD50s for Commercial PIP are 6000 mg/kg and 16,800 mg/kg, respectively. The material is irritating to the skin and causes corneal damage to the eyes. Since PIP and HEP are positive in guinea pig sensitization studies, Commercial PIP is also considered to have the potential to cause dermal sensitization.

Conclusion – No additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity
For PIP, The No-Observed-Effect-Level (NOEL) was 50 mg/kg/day in a 90-day rat study. In dogs, the No-Observed-Adverse-Effect-Level (NOAEL) was 25 mg/kg/day in a study of the same duration.

A literature search did not find any repeated dose toxicity studies of HEP or DHEP.

For Commercial PIP, the NOEL in a 7 day study was $\geq$1610 mg/kg/day. Because Commercial PIP has limited uses with a limited number of customers, it meets the criteria of a closed system intermediate as defined by the EPA. Thus no additional work is needed.

Conclusion - No further testing for this HPV Endpoint is recommended.

3.0 Developmental Toxicity
Piperazine was negative in a rat developmental study and effects observed in rabbit developmental study were attributed to maternal toxicity. There is no developmental toxicity information available for HEP, DHEP or Commercial HEP. Since Commercial HEP meets the criteria of a closed system intermediate, a developmental toxicity study needs to be conducted. The most cost effective study using the least number of animals would appear to be an OECD 421 reproduction/developmental toxicity study. Since the most likely route for human exposure is via the dermal route, a dermal reproduction/developmental toxicity study (OECD 421) is recommended.

Conclusion - A dermal reproduction/developmental toxicity study (OECD 421) is recommended.

4.0 Reproductive Toxicity
Piperazine has been reported to produce positive effects in a two generation reproductive toxicity study in rats. There is no reproductive toxicity information available for HEP, DHEP or Commercial HEP. Since Commercial HEP meets the criteria of a closed system intermediate, a reproduction study is not necessary. However as mentioned in 3.0, the most cost effective study using the least number of animals to satisfy developmental toxicity requirements would appear to be an OECD 421 reproduction/developmental toxicity study. Since the most likely route for human exposure is via the dermal route, a dermal reproduction/developmental toxicity study (OECD 421) is recommended.

Conclusion - A reproduction/developmental toxicity study (OECD 421) is recommended.

5.0 Mutagenicity and Chromosomal Aberrations
5.1 Mutagenicity Testing (Ames test)
Piperazine and DHEP have been negative in the Ames test with and without metabolic activation. In the two strains tested HEP was also negative in the Ames test under similar conditions.

5.2 - Chromosomal Aberrations
Piperazine was negative in a mouse micronucleus assay. There is no additional information available for HEP or DHEP.

Conclusion - A chromosomal aberration test (OECD 473) is recommended.

V. REFERENCES

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide).
Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES -IUCLID

Data Sets are appended

Table 1. Matrix of Available and Adequate Data on Commercial Hydroxyethylpiperazine Physicochemical Properties

Name (CAS No.)	Melting Point (°C)	Vapor Pressure (hPa @ 20°C)	Boiling Point (°C)	Partition Coefficient	Water Solubility (mg/L @ 20C)
Piperazine (PIP) (110-85-0)	107-111 (measured)	15 hPa at 50°C (measured) 0.392@22.5°C according to draft EU Risk Assessment	146-148 (measured)	-1.24 according to draft EU Risk Assessment	150,000 (measured)
Hydroxyethylpiperazine (HEP) (103-76-4)	<-10 (measured)	<0.01333 (measured) 0.02278@25C (measured)	246-246.4 (measured)	-1.56 (estimated) Epiwin supported by measured solubility in other solvents	Miscible (measured) 1,000,000 est. Epiwin
Dihydroxyethylpiperazine (DHEP) (122-96-3)	134-136 (measured)	0.0465 (measured)	310 (measured)	-1.92 (estimated)	>45% (V/V)
Commercial Hydroxyethylpiperazine	50-60 (UCC MSDS)	9.73 (UCC MSDS)	115 (UCC MSDS)	<-1.24 (based on components)	850,000 (UCC MSDS)

Table 2. Matrix of Available and Adequate Data on Commercial Hydroxyethylpiperazine
Environmental Fate

Name (CAS No.)	**Hydrolysis**	**Photodegradation (t1/2 in hours)**	**Biodegradation**	**Environmental Transport** Level III 1000 kg/hr released to air, water and soil
Piperazine (PIP) (110-85-0)	Stable to hydrolysis according to draft EU Risk Assessment	1.63 x 10-10 cm3/mol sec half life 0.8 hours	91% after 16 days in OECD 302B (measured) Inherently biodegradeable 11% after 20 days in UCC study	Air – 0.032 % Water - 69.5 % Soil - 30.4 % Sediment – 0.027 %
Hydroxyethylpiperazine (HEP) (103-76-4)	No hydrolyzable part	1.87 x 10-10 cm3/mol sec half life 0.7 hours	13% after 20 days in UCC study (measured)	Air – 0.0057 % Water - 69.6 % Soil - 30.3 % Sediment – 0.028 %
Dihydroxyethylpiperazine (DHEP) (122-96-3)	No hydrolyzable part	2.04 x 10-10 cm3/mol sec half life 0.6 hours	10% after 20 days in UCC study (measured)	Air – 0.018% Water – 72.2% Soil - 27.7% Sediment – 0.029%
Commercial Hydroxyethylpiperazine	No hydrolyzable part	Half life $\leq$ 0.8 hours	No data	No data

Table 3. Matrix of Available and Adequate Data on Commercial Hydroxyethylpiperazine Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/l)	Acute Invertebrate 48-hour EC50 (mg/l)	Algal growth inhibition EC50 (mg/l)
Piperazine (PIP) (110-85-0)	>1800 (based on draft EU Risk Assessment) 1470 (est.)	21 (based on draft EU Risk Assessment) 98.1 in UCC study 76 (est.)	>1000 (based on draft EU Risk Assessment) 54 (est.)
Hydroxyethylpiperazine (HEP) (103-76-4)	6807 (est.)	384 (measured) 317 (est.)	175 (est.)
Dihydroxyethylpiperazine (DHEP) (122-96-3)	15487 (est.)	883 (measured) 689 (est.)	336 (est.)
Commercial Hydroxyethylpiperazine	No data	No data	No data

Table 4. Matrix of Available and Adequate Data on Commercial Hydroxyethylpiperazine
Acute and Repeat-dose Toxicity

Name (CAS No.)	Acute Oral (mg/kg)	Acute Dermal (mg/kg)	Acute Inhalation (mg/L, 8 h)	Skin irritation	Eye irritation	Sensitization	Repeat Dose	Reproductive	Developmental
Piperazine (PIP) (110-85-0)	2600 (measured)	4000 (measured)	No data	Irritating (measured)	Irritating (measured)	Positive (measured)	NOEL 50 mg/kg/day in 90 day rat study NOAEL 25 mg/kg/day in 90 day dog study (Draft EU Risk Assessment)	Positive in 2-gen repro study with a tentative NOAEL of 125 mg/kg/day and a LOAEL of 300 mg/kg/day (Draft EU Risk Assessment)	Negative in rat Effects observed in rabbit attributed to maternal toxicity (Draft EU Risk Assessment)
Hydroxyethylpiperazine (HEP) (103-76-4)	~2000 (measured)	16,800 (measured)	No data	Minor irritation subsided within 7 days (measured)	Extensive corneal damage (measured)	Positive (measured)	No data	No data	No data
Dihydroxyethylpiperazine (DHEP) (122-96-3)	3.7 ml/kg 19578 mg/kg (for a 50% aqueous solution) (measured)	>10,000	No data	Minor irritation subsided within 1 day (measured)	Extensive corneal damage (measured)	No data	No data	No data	No data
Commercial Hydroxyethylpiperazine	6000	16,800	LC50 greater than saturated atmosphere	Minor irritation subsided within 2 days (measured)	Extensive corneal damage (measured)	Positive (based on components)	7 day study NOEL ≥1610 mg/kg/day (measured)	No data	No data

Table 5. Matrix of Available and Adequate Data on Commercial Hydroxyethylpiperazine Genotoxicity

Name (CAS No.)	**Genotoxicity (*in vitro* -bacterial)**	**Genotoxicity (*in vitro* - mammalian)**	**Genotoxicity (*in vivo*)**	**Carcinogenicity**
Piperazine (PIP) (110-85-0)	Negative (Draft EU Risk Assessment)	Usually negative (measured)	Negative (measured)	Negative (measured)
Hydroxyethylpiperazine (HEP) (103-76-4)	Negative in strains TA98 and TA100 with and without metabolic activation (measured)	No data	No data	No data
Dihydroxyethylpiperazine (DHEP) (122-96-3)	Negative (measured)	No data	No data	No data
Commercial Hydroxyethylpiperazine	No data Since PIP and DHEP are both negative in all strains tested and HEP is negative in two strains, CHEP would be expected to be negative in the Ames test	No data	No data	No data

Table 6
Test Plan Matrix for Commercial Hydroxyethylpiperazine

	PIP 110-85-0	**HEP (103-76-4)**	**DHEP 122-96-3**	**CHEP 12-20%PIP 38-47% HEP 16-25% DHEP 17-26% water**
PHYSICAL CHEMISTRY				
Melting point, °C	107	<10	134-136	50-60
Boiling point, °C	147.7	246-246.4	277.9	115
Vapor Pressure, hPa at 20C	0.392 @22.5C	<0.01333 (measured)		9.73
Water Solubility, mg/L	150,000	miscible	miscible	850,000
K_{ow}	-1.24	-1.56 est. Epiwin	-1.92 (calculated)	**>1.24 (based on components) R**
ENVIRONMENTAL FATE				
Biodegradation	91% after 16 days in OECD 302B 11% after 20 days in closed system	13% after 20 days in closed system	10% after 20 days in closed system	**≥10% after 20 days in closed system (based on components) R**
Hydrolysis	No hydrolyzable part	No hydrolyzable part	No hydrolyzable part	**No hydrolyzable part (based on components) R**
Photodegradability half life hours	0.8			A
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released into air, water, and soil.				A

Table 6
Test Plan Matrix for Commercial Hydroxyethylpiperazine (continued)

	PIP **110-85-0**	**HEP** **(103-76-4)**	**DHEP** **122-96-3**	**CHEP** **12-20%PIP** **38-47% HEP** **16-25% DHEP** **17-26% water**
ECOTOXICITY				
Acute Toxicity to Fish (96hr LC50)	>1800 1470 (est.)	6807 (est.)	15487 (est.)	**>1800 (based on piperazine)** **R**
Acute Toxicity to Aquatic Invertebrates (48hr EC50)	21 98.1 in UCC study 76 (est.)	384 317 (est.)	883 689 (est.)	**>21 (based on piperazine)** **R**
Toxicity to Aquatic Plants (72hr EC50)	>1000 54 (est.)	175 (est.)	336 (est.)	**>1000 (based on piperazine)** **R**
TOXICOLOGICAL DATA				
Acute Toxicity (oral), LD50	2600	~2000	~3700	6000 A
Acute Toxicity (dermal) LD50	4000	16,800	>10,000	16,800 A
Acute Toxicity (inhalation) 8 hour	No data	No data	No data	LC50 greater than saturated atmosphere A
Acute Eye Irritation	Irritating	Extensive corneal damage	Extensive corneal damage	Extensive corneal damage A
Acute Skin Irritation	Irritating	Minor irritation subsided within 7 days When applied to intact skin for 4 hours, slight to moderate erythema was observed.	Slight erythema subsided within 1 day	Minor irritation subsided within 2 days A

Table 6
Test Plan Matrix for Commercial Hydroxyethylpiperazine (continued)

	PIP 110-85-0	**HEP (103-76-4)**	**DHEP 122-96-3**	**CHEP 12-20%PIP 38-47% HEP 16-25% DHEP 17-26% water**
Sensitization	Positive	Positive	No data	**Positive (based on components)** R
Repeated Dose Toxicity	NOEL 50 mg/kg/day in 90 day rat study NOAEL 25 mg/kg/day in 90 day dog study	No data	No data	7-day NOEL >1620 mg/kg/day **NR**
Genetic Toxicity-Mutation	Negative	Negative in strains TA98 and TA100 with and without metabolic activation	Negative	**Negative (based on components) R**
Genetic Toxicity- Chromosomal Aberrations	Negative *in vitro* and *in vivo*	No data	No data	**Test CHEP**
Toxicity to Reproduction	Supposedly positive in 2-gen repro study with a tentative NOAEL of 125 mg/kg/day and a LOAEL of 300 mg/kg/day. Questions about this study have been raised in EU Risk Assessment	No data	No data	**Test OECD 421**
Developmental Toxicity	Negative in rat Effects observed in rabbit attributed to maternal toxicity	No data	No data	**Test OECD 421**

Table 6

Test Plan Matrix for Commercial Hydroxyethylpiperazine (continued)

Legend	
Symbol	**Description**
R	
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties